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SIMPLE AND HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF A 1β-METHYLCARBAPENEM KEY INTERMEDIATE INVOLVING DIVALENT TIN ENOLATES

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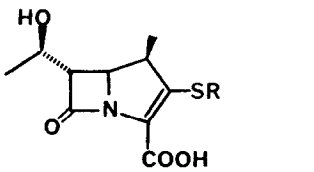
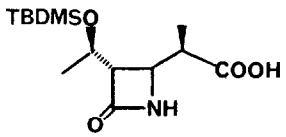
Abstract: A simple and diastereoselective synthesis of 1β-methylcarbapenem key intermediate has been accomplished via a novel C-C bond formation at the C-4 position of 4-acetoxyazetidinone 4 involving divalent tin enolates of 3-propanoyl thiazolidine and oxazolidine-2-thiones derivatives.

Carbapenems are among the most potent broad spectrum β-lactam antibiotics[1], but many of them are readily metabolized by renal dehydropeptidase-I (DHP-I). On the other hand, Merck researchers found that introduction of a methyl substituent at β C-1 position of the carbapenem nucleus resulted in an exceptional increase of stability, the 1β-methylcarbapenems 1 and 2 are good examples[2a]. However, only a few papers have appeared regarding the stereoselective introduction of the β-methyl substituent[2]. In this communication we wish to report a simple and diastereoselective synthesis of the key intermediate 3 from the readily available azetidinone 4[3].

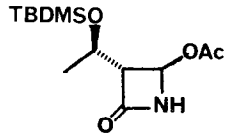


1 R=$CH_2CH_2NH_2$

2 R=CH_2 NMe_2 (NH)



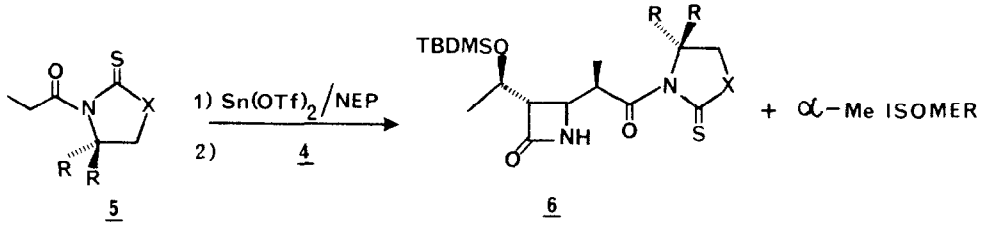
3



4

Initially, we were especially attracted to Mukaiyama's divalent tin enolates of 3-acyl thiazolidine-2-thiones[4] because of their **erythro**-selectivity in aldol type reactions and their effectiveness as an active carbonyl group for subsequent transformations. We therefore undertook to test the reaction of the divalent tin enolate of the 3-propanoyl derivative **5a** with 4 (Scheme 1, run a). The tin (II) enolate of **5a** was prepared according to Mukaiyama's procedure[4] (**5a** + N-ethylpiperidine (NEP) and $Sn(OTf)_2$ in CH_2Cl_2, -20°C → 0°C). Then an acetonitrile solution[5] of 4 was added and the reaction mixture stirred at 0°C for another 2 h. After work-up, analysis of the crude **6a** (HPLC, NMR) indicated a mixture of β and α isomers in a 6.7:1 ratio. After silica gel chromatography the pure diastereomeric mixture was obtained in 73% yield[6]. Treatment of this mixture with 1N sodium hydroxide in THF at 0°C gave the expected acid 3 (β + α) from which the stereochemistry was unambiguously assigned β by comparison with authentic sample[2a]. Seeking to improve selectivity we next tried the bulkier 4,4-dimethyl substituted derivative **5b**[7]. Under similar conditions[8a], treatment of 4 with the tin (II) enolate of **5b** gave **6b** in higher diastereoselectivity (i.e. 9:1). Purification of the latter by silica gel chromatography afforded the pure β isomer **6b** in 78% yield as a light yellow solid[8b].

SCHEME 1



5 6

run	5	β:α	Yield of 6
a	X=S, R=H	6.7:1	73%[a]
b	X=S, R=CH_3	9:1	75%
c	X=O, R=H	4:1	80%[a]
d	X=O, R=CH_3	24:1	79%

a) yield includes α isomer.

Encouraged by these results, we decided to investigate the corresponding readily available 1,3-oxazolidine-2-thiones derivatives **5c** and **5d** as auxiliaries[9]. Accordingly **5c** was treated with $Sn(OTf)_2$ and NEP in THF[10] at -20°C and, after warming to 0°C, 4 was added and the mixture stirred for 30 min. After work-up, analysis of the crude product showed a modest selectivity

of 4:1 for the desired β isomer **6c**. We next investigated the corresponding bulkier 4,4-dimethyl substituted derivative **5d**. Accordingly, **5d** (3.00 mmol) was treated with $Sn(OTf)_2$ (3.20 mmol) and NEP (3.5 mmol) in dichloromethane (6.8 mL) at 0°C for 30 min. A solution of 4 (2.0 mmol) in acetonitrile (3.4 mL) was added and the resulting mixture stirred at 0°C for 90 min. Diluted NH_4Cl solution was added and the mixture was stirred vigorously at 0°C for a few min before filtration through Celite. After extraction with EtOAc, analysis of the crude product indicated the formation of the expected intermediate **6d** with a remarkable β-diastereoselectivity of 24:1. After silica gel chromatography (CH_2Cl_2-CH_3CN 9:1) pure β isomer **6d** (>98.5%) was isolated in 79% yield as a white solid[11]. Removal of the oxazolidine-2-thione moiety of **6d** afforded the desired acid **3** in 89% yield[12].

Thus we have demonstrated that divalent tin enolates of 3-propanoyl thiazolidine and oxazolidine-2-thiones derivatives react with 4 to provide compound **6** with good β-diastereoselectivity particularly when the inexpensive and readily available derivative **5d** is used.

Acknowledgements: The authors thank Drs M. Caron and Y.G. Perron and Mr. R. Droghini for their help in preparing this manuscript.

Notes and references

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2) (a) D.H. Shih, F. Baker, L. Cama, B.G. Christensen, Heterocycles, 1984, **21**, 29; (b) L.M. Fuentes, Abstract P7-190, Tenth International Congress of Heterocyclic Chemistry, Waterloo, 1985; (c) T. Iimori and M. Shibasaki, Tetrahedron Lett., 1986, **27**, 2149; (d) T. Shibata, K. Iino, T. Tanaka, T. Hashimoto, Y. Kameyama and Y. Sugimura, ibid, 1985, **26**, 4739; (e) T. Chiba, M. Nagatsuma and T. Nakai, Chem. Lett., 1985, 1343.

3) A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, Chem. Pharm. Bull. 1981, **29**, 2899; K. Hirai, Y. Iwano and K. Fujimoto, Heterocycles, 1982, 17, 201.

4) T. Mukaiyama, N. Iwasawa, R.W. Stevens and T. Haga, Tetrahedron, 1984, **40**, 1381 and references cited therein.

5) Optimum results were obtained when acetonitrile was used as cosolvent.

6) Not separable by silica gel chromatography. However, when the diastereomeric mixutre was treated with ether at 0°C, the insoluble α isomer was easily removed to give almost pure **6a** (98%).

7) R.A. Bafford, F. Chanon, M. Chanon and J. Metzger, Bull. Soc. Chim., 1973, 971.

8) (a) Carried out as follows: 1) 5b (1.96 mmol), $Sn(OTf)_2$ (2.06 mmol), NEP (2.26 mmol) in CH_2Cl_2 (5 mL) -20°C → 0°C 35 min. 2) 4 (1.30 mmol) in CH_2Cl_2 (1 mL) 0°C 3.5 h. (b) ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.06 (s, 6H, CH_3-Si), 0.86 (s, 9H, CH_3-C-Si), 1.19 (d, 3H, J=7Hz, CH_3-C-H), 1.22 (d, 3H, J=7Hz, CH_3-C-H), 1.57 (s, 3H, CH_3-C-N), 1.63 (s, 3H, CH_3-C-N), 3.09 (dd, 1H, J=2.5, 3.5 Hz, H3), 3.20 (AB, 2H, J=11.3 Hz, CH_2-S), 4.01 (dd, 1H, J=2.5, 3.0 Hz, H4), 4.15 (m, 1H, CH_3-CH-C=O), 4.35 (m, 1H, CH_3CH-O), 5.9 (s, 1H, NH). IR (nujol) 3160, 1760, 1710 and 1300 cm^{-1}.

9) Easily prepared from their corresponding commercially available 1,2-aminoalcohols and carbon disulfide in the presence of base. Y. Nagao, T. Kumagai, S. Yamada and E. Fujita, J. Chem. Soc., Perkin Trans. 1, 1985, 2361; Y. Nagao, S. Yamada, T. Kumagai, M. Ochiai and E. Fujita, J. Chem. Soc., Chem. Commun., 1985, 1418 and references cited therein.

10) When CH_2Cl_2 was used as solvent, precipitation of the enolate occurred and it reacted sluggishly with 4.

11) Spectral data of **6d**. ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.06 (s, 6H, CH_3-Si), 0.86 (s, 9H, CH_3-C-Si), 1.20 (d, 3H, J=6.3Hz, CH_3-CH), 1.22 (d, 3H, J=6.9Hz, CH_3-CH), 1.52 (s, 3H, CH_3-C-N), 1.55 (s, 3H, CH_3-C-N), 3.09 (dd, 1H, J=2, 4Hz, H3), 3.95 (dd, 1H, J=2.3, 3.8Hz, H4), 4.16 (s, 2H, CH_2-O), 4.18 (m, 1H, CH_3-CH-C=O), 4.93 (m, 1H, CH_3-CH-O), 5.94 (s, 1H, NH). IR (nujol) 3160, 1760, 1710 and 1335 cm^{-1}.

12) To a solution of **6d** (0.90 mmol) and 30% H_2O_2 (3 mmol) in THF (6 mL) was slowly added. 1N NaOH (3 mmol) at 20°C. After a few min the mixture was washed with EtOAc, then acidified to pH 2 with conc. HCl. The white solid was collected and dried to give pure 4 in 89% yield, m.p. 141-142°C.

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